

Reproductive and Developmental Effects of Disinfection By-products in Drinking Water

John S. Reif,¹ Maureen C. Hatch,² Michael Bracken,³ Lewis B. Holmes,⁴ Bernard A. Schwetz,⁵ and Philip C. Singer⁶

¹Department of Environmental Health, Colorado State University, Fort Collins, CO 80523 USA; ²Division of Epidemiology, Columbia University, New York, NY 10032 USA; ³Department of Epidemiology and Public Health, Yale University, New Haven, CT 06510 USA; ⁴Genetics and Teratology Unit, Massachusetts General Hospital, Boston, MA 02114 USA; ⁵Environmental Toxicology Program, National Institute of Environmental Health Sciences, Research Triangle Park, NC 27709 USA; ⁶Department of Environmental Sciences and Engineering, University of North Carolina, Chapel Hill, NC 27599 USA.

Recent epidemiologic studies have reported associations between the consumption of chlorinated drinking water and reproductive and developmental effects. Here we review the available epidemiologic data, assess the hazard potential posed by exposure to disinfection by-products, identify critical data gaps, and offer recommendations for further research. The epidemiologic evidence supporting associations between exposure to water disinfection by-products (DBPs) and adverse pregnancy outcomes is sparse, and positive findings should be interpreted cautiously. The methods used during the early stages of research in this area have been diverse. Variability in exposure assessment and endpoints makes it difficult to synthesize or combine the available data. Exposure misclassification and unmeasured confounding may have led to bias in risk estimation. Future studies of reproductive outcome and exposure to chlorinated water should use improved methods for exposure assessment to 1) assure selection of appropriate exposure markers, 2) assess seasonal and annual fluctuations in DBPs, 3) assess variability within the distribution system, and 4) assess exposure through multiple routes such as bathing and showering, as well as consumption. Population-based studies should be conducted to evaluate male and female fertility, conception delay, growth retardation, and specific birth defects. The reproductive and developmental effects of exposure to DBPs could be efficiently explored in ongoing investigations by incorporating valid exposure markers and relevant questionnaire information. Future studies should make use of naturally occurring variability in the concentrations of DBPs and may incorporate biomarkers of exposure and effect in their design. Epidemiologic investigations should be conducted in parallel with laboratory-based and animal studies in a coordinated, multidisciplinary approach. *Key words:* birth defects, chlorination, drinking water, epidemiology, low birth weight, prematurity, reproduction, teratogens, trihalomethanes. *Environ Health Perspect* 104:1056–1061 (1996)

Chlorination is the major method of water disinfection used worldwide (1). Thus, much of the health research on the disinfection by-products (DBPs) found in drinking water has been conducted on by-products of chlorination, especially the trihalomethanes (THMs). This research encompasses animal bioassays for cancer and noncancer health effects (1,2) and epidemiologic studies evaluating carcinogenicity (3) or reproductive toxicity (2). A maximum contaminant level (MCL) of 100 µg/l for the THMs, one of the major groups of chlorination by-products, was established in 1979 by the U.S. Environmental Protection Agency (EPA). Since 1979, other by-products have been identified from the process of chlorination and, to some extent, from chloramination, chlorine dioxide disinfection, and ozonation.

Recently, four epidemiologic studies have reported associations between the consumption of chlorinated drinking water and reproductive or developmental effects. Here we review the available epidemiologic data, assess the hazard potential suggested by the available data, identify critical data gaps,

and offer recommendations for further short- and long-term research.

Epidemiologic Studies

The first study designed specifically to evaluate the effect of exposure to DBPs on human reproductive outcome was conducted among residents of small towns in Iowa (4). Population-based case-control analyses were performed to determine whether water supplies containing relatively high levels of chloroform and other THMs were associated with low birth weight, prematurity, or intrauterine growth retardation (IUGR). Exposures to THMs were estimated from a municipal water survey conducted 2 years previously.

Residence in communities where chloroform concentrations exceeded 10 µg/l was associated with increased risk for IUGR [odds ratio (OR) = 1.8] (Table 1). The risk estimate for IUGR and dichlorobromomethane concentrations ≥ 10 µg/l was also elevated (OR = 1.7) (4). The major limitation of the Iowa study was in the assessment of trihalomethane exposure,

including imprecision introduced by using municipal surveys to assign exposure to individuals and the potential for misclassification arising from fluctuations in THM levels over time and from residential mobility.

A cross-sectional study was conducted in four counties in northern New Jersey to search for associations between selected developmental and reproductive outcomes and contaminants found in public water supplies (5,6). Birth weight, fetal deaths, and birth defects were evaluated by linking quarterly THM measurements and water source information collected by utilities with vital records and a birth defects registry. Flow weighting for multiple sources and forward-backward averaging techniques were used to estimate monthly THM exposures during pregnancy (5).

Positive, but small, associations with exposure to THMs at levels exceeding 80 µg/l in the municipal supply corresponding to the maternal address on the birth certificate were found for term low birth weight (OR = 1.3) and small for gestational age

Address correspondence to D. Robinson, Risk Science Institute, ILSI, 1126 16th St. NW, Washington, DC 20036 USA. M. C. Hatch is currently at Mount Sinai School of Medicine, New York, NY 10029 USA; B. A. Schwetz is currently at the National Center for Toxicological Research, Food and Drug Administration, Jefferson, AR 72079 USA.

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Table 1. Summary of adjusted relative risks (95% confidence intervals) from four epidemiologic studies of disinfection by-products and developmental outcomes

Effect	Iowa ^a	New Jersey ^b	Massachusetts ^c	North Carolina ^d
Birth defects				
All sentinel anomalies	—	1.5 (1.1–2.1) <i>n</i> = 67	1.5 (0.7–2.1) <i>n</i> = 1,039	—
Central nervous system defects	—	2.5 (1.4–4.5) <i>n</i> = 18	—	—
Neural tube defects	—	3.0 (1.3–7.1)* <i>n</i> = 8	—	—
Major cardiac defects	—	1.8 (1.0–3.6)* <i>n</i> = 12	—	—
Oral cleft defects	—	1.7 (0.9–3.4)* <i>n</i> = 11	—	—
Developmental disorders				
Birth weight <2,500 gms	1.3 (0.8–2.2) <i>n</i> = 25	1.3 (1.1–1.5) <i>n</i> = 170	—	1.3 (0.8–2.1) <i>n</i> = 57
Birth weight <1,500 gms	—	0.9 (0.6–1.2) <i>n</i> = 61	—	—
Growth retardation	1.8 (1.1–2.9) <i>n</i> = 32	1.1 (1.0–1.3) <i>n</i> = 705	—	—
Preterm delivery	1.1 (0.7–1.6) <i>n</i> = 39	1.0 (0.9–1.1) <i>n</i> = 601	—	0.9 (0.6–1.5) <i>n</i> = 62
Miscarriage	—	—	—	1.2 (0.6–2.4) <i>n</i> = 46
Stillbirth	—	0.7 (0.4–1.2) <i>n</i> = 29	2.6 (0.9–7.5) <i>n</i> = 77	—

n, number of cases in the exposure stratum.

*Unadjusted odds ratio.

^aCase-control study with exposure to chloroform (≥ 10 $\mu\text{g/l}$); data from Kramer et al. (4).

^bCross-sectional study with exposure to THM (>80 $\mu\text{g/l}$); data from Bove et al. (5).

^cCase-control study with exposure to chlorinated water (source); data from Aschengrau et al. (8).

^dCase-control study with exposure to THM (>81.1 or >82.8 $\mu\text{g/l}$); data from Savitz et al. (9).

(SGA; OR = 1.1) (5). The ORs rose to 1.4 and 1.5, respectively, for exposure to THMs at levels exceeding 100 $\mu\text{g/l}$ (6). No associations were found for very low birth weight, preterm birth, and fetal death. A mean decrease in term birth weight of 70 grams was associated with total THM exposure above 100 $\mu\text{g/l}$ (6).

Elevated adjusted odds ratios were found for several birth defects at THM concentrations ≥ 80 $\mu\text{g/l}$, as shown in Table 1: all surveillance defects (OR = 1.5), central nervous system defects (OR = 2.5), neural tube defects (OR = 3.0), oral cleft defects (OR = 1.7), all cardiac anomalies (OR = 1.4); and major cardiac defects (OR = 1.8) (5). In these analyses, the number of cases in the highest exposure stratum (≥ 100 $\mu\text{g/l}$) was often small (6). In general, strong dose-response relationships between total THM concentration and reproductive effects were not found (5,6) although a positive test for trend ($p < 0.05$) supported trends for some outcomes (6). The lack of monotonic dose-response trends may have been due, in part, to misclassification of exposure at intermediate levels of THM (6). Alternatively, lack of increase in effect with increasing levels of exposure may indicate that the associations are not causal.

The study base for the New Jersey cross-sectional study was used to identify

cases and controls for an interview-based study of cardiac, neural tube, and oral cleft defects, very low birth weight ($<1,500$ g), and low birth weight (1,500–2,499 g) (7). However, the findings from this study were affected by selection bias due to differential participation across socioeconomic and racial strata. Interviews were obtained from only 52% of the subjects selected, leading to estimates away from the null value for THM and surface water source (7). Thus, selection bias limits the interpretability of the case-control study.

A case-control approach was used to analyze data from a study of 14,130 pregnant women who delivered at Brigham and Women's Hospital in Boston, Massachusetts, between 1977 and 1980 (8). The interview included questions about the source of drinking water. The hospital record was used to determine a woman's residence during pregnancy and to identify the presence of major malformations, minor anomalies and normal variants, and other late adverse pregnancy outcomes such as stillbirth and neonatal death.

Information about the quality of drinking water was obtained from routine analyses of both chemical and metal content of the public water in Massachusetts. The source of the drinking water was determined to be surface, ground, or mixed. In

Massachusetts, all surface water is treated by either chlorination or chloramination; ground water is usually not treated (8). Risks from exposure to water quality variables on congenital anomalies ($n = 1,039$), anomalies of specific organ systems, stillbirth ($n = 77$), and neonatal death ($n = 55$) were evaluated. After adjusting for confounding, an increase in risk was found for stillbirths associated with chlorination of the community supply (OR = 2.6), with chloramination serving as the reference group. Chlorination was also associated with an increased risk for major malformations (OR = 1.5), which consisted primarily of increases in the risk of respiratory and urinary tract defects (8).

Recently, Savitz et al. (9) used data from a population-based case-control study of miscarriage, preterm delivery, and low birth weight to evaluate risk associated with water source, amount, THM concentration, and THM dose ($\mu\text{g/l} \times$ glasses of water per day). Medically treated miscarriage cases were identified through medical care providers; preterm deliveries and low birth weight infants were identified at six area hospitals, which also served as a source for the controls. Women were assigned to one of five public water supplies serving the region, and the dates of pregnancy were used to assign the THM concentration to the nearest quarterly average for that supplier. The fourth week of pregnancy was used for assigning exposure for miscarriage cases and the 28th week for preterm delivery and low birth weight cases.

Some indication of an association between THM concentration and miscarriage was found, particularly among women in the highest exposure sextile (OR = 2.8, 95% CI = 1.1–2.7). This subgroup was largely responsible for an association with a continuous measure of THM exposure (OR = 1.7 per 50 ppb increment). A small increase in risk of low birth weight (ORs = 1.3–1.5) was found for the upper two tertiles of THM exposure, compatible with the increases reported in the previous studies of this outcome (4,5). Preterm delivery was unrelated to THM concentration.

Critique

As a group, these studies suffered from a number of methodologic weaknesses that limit the interpretability of the findings. The four studies used different methods for classification of exposure: THM (6,9); concentrations of specific THMs such as chloroform (4); chlorinated or chloraminated systems (8); water source [ground, surface, or mixed (6,8) and well, community, or bottled (9)]. Surface waters typically contain higher concentrations of THMs and other

chlorination by-products due to the higher concentrations of humic substance precursors (10).

THMs represent a class of four compounds: chloroform, dibromochloromethane, dibromochloromethane, and bromoform. By using the aggregate THM concentration in an exposure assessment, we assume that the distribution of the four THM species is the same in all water samples or that all of the four species have the same reproductive impact. Moreover, chloroform and the other THM species comprise only one class of DBPs generated during water chlorination. Increased risk for reproductive and developmental disorders may be associated with other halogenated DBPs that were not analyzed.

A major weakness in this series of studies was in the exposure assessment. Typically, water quality data represented estimated community-wide concentrations, rather than residential concentrations and individual exposures. Information on amount of home tap water consumption, use of bottled water, etc., was not available. Assignment of a single THM exposure concentration for the entire 37-week gestation period more than likely misclassified exposure, as THM concentrations are known to vary seasonally, increasing with increasing temperature (11). Depending upon the variability of some sources, THM concentrations can vary appreciably on a weekly and, in some cases, even on a daily basis. Further misclassification of exposure was introduced by a temporal disparity between the collection of outcome and exposure data (4), by collecting a large proportion of the water samples for THM analysis in a single season (4), and by assuming that the average of THM measurements at four sampling locations in the distribution system reflected the THM concentration at all residences throughout the system (4,6). THM concentrations increase with time in the distribution system; therefore, populations located further from the treatment plant, from a hydraulic residence time standpoint, tend to be exposed to higher THM concentrations (12). Knowledge of the flow patterns and residence time distribution within the system are critical components of a sound exposure assessment analysis.

Several assumptions, inherent in exposure assessment in New Jersey (5), apply to the other studies as well: 1) that residence on the birth certificate represented the mother's residence during her entire pregnancy; 2) that drinking water supply to the home came from the municipal supply and not a private well; 3) that water supply to the home did not have an activated charcoal filtering system; 4) that the mother drank

and bathed primarily from the home water supply; 5) that the mother drank tap water rather than bottled water; and, 6) that contaminant levels for the sample date represented the entire town's system for a period around that date. In addition, migration during pregnancy may introduce misclassification of exposure. In a case-control study of congenital malformations in California, 25% of women moved at least once between conception and delivery (13).

Several of these assumptions are unlikely to change the general direction or magnitude of the risk estimates. For example, use of adequately maintained activated charcoal filters is likely to be uncommon. On the other hand in central North Carolina, use of a private well was reported by 24% of the participants (9), and at least some bottled water was consumed by 24% of women in a study of spontaneous abortions in California (14). Thus, lack of data for migration, private well use, and bottled water consumption may introduce substantial exposure misclassification.

The degree to which investigators were able to control for potential confounding varied across the studies. Incomplete control for confounding by cigarette smoking may have introduced bias. Maternal smoking, especially when it occurs in the third trimester, is the strongest known environmental risk factor for IUGR (15). Other variables that were unavailable for inclusion as potential confounders in some studies included socioeconomic status, alcohol consumption, maternal occupation, other environmental exposures, and reproductive history.

These studies screened a number of potential associations between DBPs found in public water supplies and developmental and reproductive outcomes. The positive findings form a foundation for further studies but should be interpreted cautiously for the following reasons: exposure misclassification probably occurred to some extent in each study; unmeasured confounding could have introduced bias leading to underestimation or overestimation of effects of exposure; and associations could be chance occurrences.

Assessment of Hazard Potential and Critical Data Gaps

The epidemiologic evidence regarding associations between exposure to water DBPs and adverse pregnancy outcomes is extremely sparse. The results from the four epidemiologic studies to date dealing directly with water disinfection are summarized in Table 1. The methods used during the early stages of research in this area have been diverse; no single study or group of

studies supports a strong interpretation. Moreover, variability in exposure assessment and endpoints makes it difficult to synthesize or combine the available data.

The studies from Iowa (4) and New Jersey (5,6) evaluated indices of fetal growth. Although definitions and standards varied, the magnitude of the observed associations with fetal growth was similar [OR = 1.5 to 1.8 for SGA at THM ≥ 100 $\mu\text{g/l}$ (6) or chloroform ≥ 10 $\mu\text{g/l}$ (4)]. Three studies evaluated the risk of low birth weight [$< 2,500$ g (4,5,9)]; an OR of 1.3 was reported in each study. Congenital malformations were considered in the New Jersey (5,6) and Massachusetts (8) studies. While two- to threefold increased risks for certain defects were observed in the New Jersey study (6), estimates for specific defects were based on small numbers of exposed cases and were unstable. Miscarriage (9) and stillbirth (8) were evaluated as an outcome in only one study each.

Data on human exposure to DBPs and effects on female and male fecundity and couple fertility are lacking entirely. There is evidence from studies in laboratory animals that the halogenated acetic acids affect spermatogenesis adversely (2), but this has not been addressed in human populations. Because the correspondence between target endpoints in humans and experimental species is stronger for reproduction than for development, the absence of data on exposed men is noteworthy. Female reproductive function has not been studied either in laboratory animals or epidemiologically.

In addition to a paucity of human data, animal data that could provide a mechanistic rationale for hypothesizing adverse effects of DBPs on reproduction and development is generally sparse. The lack of animal data upon which to evaluate biological plausibility adds to the difficulty in interpreting weak statistical associations. Additional studies of effects of exposure to DBPs in laboratory models are in progress and may aid in establishing the framework of biological plausibility.

Finally, recent epidemiologic investigations have focused on exposure to THMs which represent only one class of halogenated disinfection by-products. Other classes of DBPs are found in chlorinated drinking water, but these have not been measured on a regular basis and their health effects in humans are, for the most part, unknown.

Research Recommendations

In this section, we describe a series of short-term projects that could strengthen interpretation of existing studies and guide design of subsequent work. We also describe prerequisites for future studies on

DBPs and selected reproductive and developmental endpoints.

Short-term Research in Humans

Refining studies using existing databases. Large vital record databases and routine utility monitoring for DBPs makes it likely that additional data linkages will be pursued, despite the relative weakness of the findings to date. Recommendations to strengthen future epidemiologic studies of this genre are as follows:

Where feasible, population-based studies should make use of large natural variations in the concentrations of DBPs to maximize the likelihood of detecting potential effects. Areas where standard chlorination or alternative methods of water disinfection are practiced on either ground or surface water sources provide a setting to evaluate variation in the levels of contaminants. Areas with a high natural concentration of bromine in surface water provide an opportunity to evaluate the brominated by-products.

Methods for measuring exposure to THMs and other DBPs should be improved and standardized. Validation of exposure data collected at the municipal system-wide level should be conducted using tapwater samples taken in subjects' homes. Because this is only feasible, at best, several months to 1 year after conception, predictive models for quantifying tapwater concentrations retrospectively, over the time period of interest, are needed.

Assumptions about maternal exposure to DBPs in cross-sectional studies should be validated (i.e., residential mobility during pregnancy, level of tap and bottled water consumption, assessment of frequency and duration of bathing, use of water filter systems). Birth certificate data including adequacy of prenatal care and socioeconomic status also require validation.

Future studies of congenital malformations should consider ascertainment of birth defects where the pregnancy may be electively terminated, and heterogeneity of conditions represented in the same rubric of the International Classification of Diseases codes in birth defect registry data should be considered.

Strengthening studies designed to collect new data. In addition, we recommend consideration of the following issues when new studies are undertaken by case-control or cohort methods: 1) Rapid ascertainment of cases and controls to permit contemporaneous measures of exposure to DBPs; 2) attention to tracing a large proportion of the study population and to other factors affecting participation rates; 3) collection of information by interview to permit control of potential confounding and evalua-

tion of interaction by factors such as cigarette smoking, alcohol consumption, and drug use; and 4) development of specific biomarkers for exposure to DBPs and for the evaluation of male and female fertility and reproductive effects in cohort studies.

Improving exposure assessment. Future epidemiologic studies of exposure to by-products of water disinfection and reproductive outcomes should use more precise methods of exposure assessment:

- Selection of appropriate exposure markers for DBP toxicity. THM is often selected as a surrogate marker because it is routinely measured in public drinking water supplies for municipalities of more than 10,000 persons. Other candidates include chloroform and dibromochloromethane (among the THMs), halogenated acids, and haloacetonitriles and aldehydes.

- Adequate sampling to assess temporal and spatial variability in the concentrations of contaminants within the distribution system for each municipality in the study. This is not a trivial task and requires comprehensive knowledge of the source(s) of water utilized, type of treatment provided, residence time patterns in the distribution system, and variability in all three factors. Selection of water systems that are relatively simple and that have done extensive water quality and/or distribution system modeling and analysis might be necessary for a sound exposure assessment.

- Evaluation of exposure to DBPs in communities that receive water from mixtures of ground and surface water sources.

- Interviews with subjects to collect relevant data concerning patterns of water use and routes of exposure, including bathing, showering, and consumption.

Adding evaluation of water quality to studies in progress. An expeditious approach to conducting more definitive research on reproductive and developmental effects of exposure to DBPs involves identifying ongoing, well-designed prospective studies of other exposures and adding a component on DBP exposure parameters and water quality. This approach could generate high quality data with a minimal investment of resources. In a series of case-control studies of drinking water exposure and spontaneous abortion in California, the investigators found sufficient evidence of recall bias to recommend that a prospective study design would be preferred (16).

Longer-term Research in Humans

Standardized Methods for Assessing Exposure to Drinking Water Contaminants. Water utility companies should be active participants in study design. Maps incorporating sampling locations and points of

entry of treated water into the distribution system can be used to model exposure to individual homes. Residences could be assigned a weighting factor based on distance from sampling stations. Additional refinements of the exposure model may use pipe diameters to sampling stations, computer models of flow in the distribution system, or estimates provided by utility personnel. Samples should be collected from a sample of the subject households for model validation.

Ingestion is not the sole source of exposure to DBPs. Some by-products, primarily THMs, are volatile, and several studies suggest that inhalation is a major route of exposure for chloroform (17). Exposure to DBPs can also occur by dermal absorption. Total exposure can be estimated by collecting information on daily quantity of tap water consumed, number and duration of showers (baths) per week, and ventilation and size of shower/bathroom (18).

Monthly average exposures should be calculated using the measured quarterly DBP values and a forward- and backward-averaging technique as used in New Jersey (5) and North Carolina (9). For larger utilities, monthly THM measurements may be available to permit a more accurate quantitation of exposure. Samples should be collected and analyzed using standardized laboratory and quality assurance procedures. The concentrations of individual THM species should be reported and analyzed independently, rather than aggregate THM concentrations. With the anticipated establishment of monitoring requirements for other DBPs, e.g., the haloacetic acids, a similar approach should be implemented.

Methods for investigating selected endpoints: human fertility studies. The extant animal literature, albeit sparse, suggests that some priority be given to fecundity and fertility in future epidemiologic studies. In the following section, we suggest preliminary approaches to assess these endpoints.

An investigation of the effect of occupational exposure to compounds such as the halogenated acetic acids might be conducted through exploration of company records or by conducting semen analyses of men with high occupational exposures. Standardized semen collection and analysis procedures should be used to evaluate sperm concentration, motility, and morphology and linked to reproductive history. Occupational studies of reproductive function and fertility of female workers should parallel the male occupational studies and elicit information about pregnancy history, menstrual history, and perceived problems with menstruation and fertility.

A second, relatively efficient approach is to conduct nested case-control studies in infertility clinic populations. Men and women with specific forms of infertility could be assessed for exposure to water contaminants at home and at work. For example, men with abnormalities in sperm concentration, motility, or morphology would comprise case groups, while men with normal sperm parameters would form a control group. Interview data on sources, routes and degree of exposure to DBPs, as well as potential confounders would be collected by interviewers blinded to both exposure and fertility status.

The evaluation of conception delay, the time from first unprotected coitus to conception, is recommended as an endpoint for incorporation into existing or planned studies. This outcome has been found to be perturbed in response to exposure to recent use of oral contraceptives (19), cigarettes (20), and caffeine (21). The extent to which conception delay reflects underlying difficulty in conception, failure of implantation, or an increased risk of very early spontaneous abortion is unclear.

Growth retardation. Previous studies have suggested that a small increase in the frequency of IUGR may be associated with exposure to DBPs (4,6); however, IUGR is affected by many variables that should be considered in future studies.

Is the correlation of IUGR with birth weight only, or with birth weight, body length, and head size? Future studies should use resources that provide all measurements so the precise nature of the effect can be determined. The information on IUGR obtained should be specific for the gestational age, ethnicity, and sex of the infant. The accuracy of information on the gestational age of the infant should be assessed and, whenever possible, subdivided into those estimates based on prenatal ultrasonography and those based on the mother's reported last menstrual period.

One widely used definition of growth retardation is a birth length or weight less than the tenth centile of normal for infants of the same race, sex, and gestational age. If a definition such as the tenth centile of normal is used, it should be noted whether an effect is seen when a more rigorous definition (e.g., the 2.5th centile of normal) is applied. Investigators should choose an external standard appropriate for the population being studied.

Many medical disorders are associated with growth retardation. Passive systems of reporting, such as birth certificates, cannot be relied upon to identify these potentially important confounders.

Common malformations. The studies reviewed above suggest that exposure to DBPs may increase the rates of occurrence for three common groups of malformations: neural tube defects, major heart defects, and oral cleft defects (6). Future studies of these associations should be based on larger sample sizes and address the issues described below.

Investigators should focus on specific malformations and avoid the use of broad categories based on organ systems, such as ear, face, and neck, or musculoskeletal. Nonspecific categorization schemes treat a diverse group of phenotypes that would be expected to have different etiologies as a single outcome. Teratogenicity of thalidomide was only identified in the Swedish birth defects registry when the analysis was restricted to infants with preaxial and symmetrical limb deficiencies rather than all types of limb defect (22).

Common malformations such as neural tube defects (23) and heart defects (24) are heterogeneous with respect to both phenotype and presumed etiology. Passive systems of reporting birth defects, such as birth certificates and hospital discharge summaries, list only a single diagnosis and do not provide sufficient detail upon which to form homogeneous groupings. In addition, the presence of subtle chromosome abnormalities is not always noted in these passive systems.

A significant portion of infants with spina bifida are currently diagnosed by prenatal screening and the pregnancies terminated electively (25). Studies of only live-born infants with spina bifida will be incomplete and subject to selection bias; significant differences exist in socioeconomic status between infants diagnosed prenatally and postnatally. Consideration should be given to identifying infants with spina bifida, anencephaly, and encephalocele through prenatal diagnosis programs, as well as through hospitals where affected live-born and stillborn infants are delivered.

Subdividing birth defects by anatomical and genetic characteristics will provide a more homogeneous group for analysis; however, larger numbers of cases will be required to identify homogeneous subsets of defects and maintain statistical power. Thus, costs may increase unless the study can be incorporated into an ongoing surveillance system.

Conclusions

Epidemiologic understanding of exposure-disease relationships generally evolves through an iterative process in which successive studies attempt to extend and improve upon earlier reports. Epidemiologic research on DBPs in drinking water and reproduc-

tive effects is at a very early stage, and it is not surprising to find that the studies conducted to date employed relatively inexpensive, expedient methods. Early stage studies often rely on available data rather than on gathering new information or undertaking individual exposure assessment. As a result, data on important variables may be poorly measured or lacking entirely. Small increases in risk may be due to chance, confounding, or bias. While studies of this type may be appropriate when knowledge about an issue is limited and may be useful in suggesting additional research directions, such studies do not form an adequate empirical base from which to take a position for or against risk or causality.

There is little question that water disinfection is desirable, and, as yet, there is no indication that alternatives to chlorination are themselves without potential risk. The currently available human studies on effects of chlorination by-products provide an inadequate basis for identifying DBPs as a reproductive or developmental hazard. Nevertheless, additional laboratory animal and epidemiologic research should be conducted, employing a coordinated multidisciplinary approach. Animal studies may suggest appropriate endpoints for study in human populations, in addition to those outcomes routinely measured in vital statistics data, or may be used to develop biomarkers that could be incorporated into studies of human populations. Laboratory research focused on risk assessment to include hazard identification, dose response, comparative disposition and pharmacokinetics, and mechanisms and modes of activities should be conducted in parallel with epidemiologic studies. Human studies may suggest critical periods prior to, or following, conception for experimental evaluation or may identify additional by-products that merit intensive laboratory investigation. Expertise in broad areas of water source, treatment, chemistry, and engineering (26), as well as disciplines such as reproductive biology, may shed important new light on this developing area of public health research.

REFERENCES

1. IARC. IARC monographs on the evaluation of carcinogenic risk to humans, vol 52. Chlorinated drinking water; chlorination by-products; some other halogenated compounds; cobalt and cobalt compounds. Lyon:International Agency for Research on Cancer, 1991.
2. EPA/ILSI. A review of evidence on reproductive and developmental effects of disinfection by-products in drinking water. Washington:U.S. Environmental Protection Agency and International Life Sciences Institute, 1993.

3. Morris RD, Audet AM, Angelillo IF, Chalmers TC, Mosteller F. Chlorination, chlorination by-products, and cancer: a meta-analysis. *Am J Public Health* 82:955-963 (1992).
4. Kramer MD, Lynch CF, Isacson P, Hanson JW. The association of waterborne chloroform with intrauterine growth retardation. *Epidemiology* 5:407-413 (1992).
5. Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Zagraniski RT. Report on phase IV-A: public drinking water contamination and birth weight, fetal deaths and birth defects: a cross-sectional study. Trenton, NJ:New Jersey Department of Health, 1992.
6. Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. Public drinking water contamination and birth outcomes. *Am J Epidemiol* 141:850-862 (1995).
7. Bove FJ, Fulcomer MC, Klotz JB, Esmart J, Dufficy EM, Savrin JE. Report on phase IV-B: public drinking water contamination and birth weight, and selected birth defects: a case-control study. Trenton, NJ:New Jersey Department of Health, 1992.
8. Aschengrau A, Zierler S, Cohen A. Quality of community drinking water and the occurrence of late adverse pregnancy outcomes. *Arch Environ Health* 48:105-113 (1993).
9. Savitz DA, Andrews KW, Pastore LM. Drinking water and pregnancy outcome in central North Carolina: source, amount and trihalomethane levels. *Environ Health Perspect* 103:592-596 (1995).
10. McGuire MJ, Meadow RG. AWWARF trihalomethane survey. *J Am Water Works Assoc* 80:61-68 (1988).
11. Singer PC, Barry JJ, Palen GM, Scrivner AE. Trihalomethane formation in North Carolina drinking waters. *J Am Water Works Assoc* 73:392-401 (1981).
12. Symons JM, Stevens AA, Clark RM, Geldreich EE, Love OT Jr, DeMarco J. Treatment techniques for controlling trihalomethanes in drinking water. U.S. EPA 600/2-81-156. Washington:U.S. Environmental Protection Agency, 1982.
13. Shaw GM, Malcoe LH. Residential mobility during pregnancy for mothers of infants with or without congenital cardiac anomalies. *Arch Environ Health* 46:310-312 (1991).
14. Hertz-Picciotto I, Swan SH, Neutra RR, Samuels SJ. Spontaneous abortions in relation to consumption of tap water: an application of methods from survival analysis to a pregnancy follow-up study. *Am J Epidemiol* 130:79-93 (1989).
15. Bracken MB, Belanger K, Hellenbrand K, Dlugosz L, Holford TR, McSharry JE, Addesso K, Leaderer B. Exposure to electromagnetic fields during pregnancy with emphasis on electrically heated beds: association with birth weight and intrauterine growth retardation. *Epidemiology* 6:263-270 (1995).
16. Neutra RR, Swan SH, Hertz-Picciotto I, Windham GC, Wrensch M, Shaw GM, Fenster L, Deane M. Potential sources of bias and confounding in environmental epidemiologic studies of pregnancy outcomes. *Epidemiology* 3:134-142 (1992).
17. Maxwell MI, Burmaster DE, Ozonoff D. Trihalomethanes and maximum contaminant levels: the significance of inhalation and dermal exposures to chloroform in household water. *Regul Toxicol Pharmacol* 14:197-312 (1991).
18. Jo WK, Weisel CP, Liroy PJ. Chloroform exposure and the health risk associated with multiple uses of chlorinated tap water. *Risk Anal* 10:581-585 (1990).
19. Bracken MB, Hellenbrand KG, Holford TR. Conception delay after oral contraceptive use: the effect of estrogen dose. *Fertil Steril* 53:21-27 (1990).
20. Baird DD, Wilcox AJ. Cigarette smoking associated with delayed conception. *JAMA* 253:2979-2983 (1985).
21. Hatch EE, Bracken MB. Association of delayed conception with caffeine consumption. *Am J Epidemiol* 138:1082-1092 (1993).
22. Kallen B, Rahmani TM-Z, Winberg J. Infants with congenital limb reduction registered in the Swedish register of congenital malformations. *Teratology* 29:73-85 (1984).
23. Holmes LB, Driscoll S, Atkins L. Etiologic heterogeneity of neural tube defects. *N Engl J Med* 294:365-369 (1976).
24. Amati, F. Mari A, Digilio MC, Mingarelli R, Marino B, Giannotti A, Novelli G, Dallapiccola B. 22q11 deletions in isolated and syndromic patients with tetralogy of Fallot. *Hum Genet* 95:479-482 (1995).
25. Roberts HE, Moore CA, Cragan JD, Fernhoff PM, Khoury MJ. Impact of prenatal diagnosis on the birth prevalence of neural tube defects, Atlanta, 1990-1991. *Pediatrics* 96:880-883 (1995).
26. Singer PC. Control of disinfection by-products in drinking water. *J Environ Eng* 120:727-744 (1994).

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For further information:

Conference Secretariat, Ortra Ltd., 2 Kaufman Street, PO Box 50432, Tel Aviv 61500, Israel
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